REMARKS

The Amendment, filed in response to the Office Action mailed June 9, 2009, is believed to address all issues raised in the Action. Favorable reconsideration is respectfully requested in view of Applicant's remarks herein.

Claim Status

In the Amendment, claim 13 is amended to more clearly set forth the claimed subject matter of the present invention. Support for the amendment of claim 13 can be found, for example, at pages 8, line 16 - page 11, line 13, and page 13, line 5 - page 20 and claims 14-19.

Additionally, the specification has been amended to correct a translation error on page 8, line 6. The term "disseminated meningitis" should have been correctly translated to "meningeal dissemination" as is supported by the context of the entire paragraph bridging pages 7 - 8 in the specification. The foreign priority document of Japanese Patent Application No. 2002-094313, of which a certified copy was submitted on September 27, 2004, also supports the correctly translated term. See page 7, lines 12-15 of the priority document. No new matter is introduced.

Claims 1-19 are all the claims pending in the application, of which claims 1-12, and 14-17 are withdrawn from consideration. It is noted that the Examiner asserts claim 19 is drawn to a non-elected invention. Applicant respectfully submits that claim 19, which refers to claim 13, recites the elected compound, 7-acetyl-5-(4-aminophenyl)-8(R)-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine, in lines 18-19 of claim 19. Therefore, claim 19 encompasses the elected compound and it is respectfully requested that claim 19 is considered to the extent it reads on the elected compound.

Response to Rejection under 35 U.S.C. § 112, first paragraph

On page 3 of the Action, claims 13 and 18 are rejected under 35 U.S.C. 112, first paragraph, because allegedly the specification, while being enabling for *in vitro* treatment of glioblastoma does not reasonably provide enablement for *in vivo* treatment of glioblastoma with each and every compound claimed.

Applicant thanks the Examiner for recognizing the *in vitro* correlation of AMPA antagonist, in view of Applicants' arguments and supporting evidence. The Examiner, however, now asserts that correlation of *in vitro* and *in vivo* results is not established in terms of predictability. The Examiner alleges that the previous Declaration filed on March 20, 2009 does not provide *in vivo* results of any or every or all AMPA antagonists which exist in the pharmaceutical art in providing *in vivo* treatment of glioblastoma and the Declaration is not commensurate with the scope of claim.

Applicant respectfully traverses.

Without acquiescing or agreeing with the Examiner's position, solely in order to compact the prosecution of the application, Claim 13 has been amended to recite specific AMPA antagonists, for which *in vitro* and *in vivo* data of effectiveness are provided, or *in vitro* data of effectiveness are presented, by way of the original disclosure of the specification, the previously submitted Rule 132 Declaration, and/or currently submitted Second Rule 132 Declaration.

Specifically, amended claim 13 recites a method for treating glioblastoma comprising administering a compound having an AMPA antagonist activity wherein the compound is [7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-3,4-dihydroquinoxalin-1(2H)-yl]acetic acid (Compound A); 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)-quinoxaline (NBQX); 2-[N-(4-chlorophenyl)-N-methylamino]-4H-pyrido[3,2-e]-1,3-thiazin-4-one (Compound B); 1-(4-aminophenyl)-4-

methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (GYKI 52466), or 7-acetyl-5-(4-aminophenyl)-8(R)-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (Talampanel).

The correlation of *in vitro* and *in vivo* data of each compounds are as follows:

With regard to [7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-3,4-dihydroquinoxalin-1(2H)-yl]acetic acid (Compound A), submitted herewith is a copy of Nature Medicine, 8(9), 971-978 (2002) by Ishiuchi et al. in which *in vitro* experimental results of Compound A can be found at page 974 in the right column.[1] (See also the Rule 1.132 Declaration submitted herewith). *In vivo* experimental results of Compound A can be found in Example 2 of the specification.

With regard to 2-[N-(4-chlorophenyl)-N-methylamino]-4H-pyrido[3,2-e]-1,3-thiazin-4-one (Compound B), *in vitro* experimental results of Compound B can be found in Test 1 submitted in the Rule 1.132 Declaration filed on March 20, 2009. *In vivo* experimental results of Compound B are shown in Test 2 of the Rule 1.132 submitted herewith.

With regard to 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (GYKI 52466), *in vitro* experimental results of GYKI 52466 can be found in Test 2 submitted in the Rule 1.132 Declaration filed on March 20, 2009. *In vivo* experimental results of GYKI 52466 are shown in Test 3 of the Rule 1.132 submitted herewith.

With regard to 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)-quinoxaline (NBQX), *in vitro* experimental results of NBQX can be found in Example 1 of the specification.

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[1] This document is submitted as evidence directed to an issue of patentability raised in the Office Action, and the evidence is timely presented, thus the Applicant need not submit an IDS in order for the Examiner to consider the document. See MPEP 609.05(c).

With regard to 7-acetyl-5-(4-aminophenyl)-8(R)-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (Talampanel), *in vitro* experimental results of Talampanel can be found in Test 3 submitted in the Rule 1.132 Declaration filed on March 20, 2009.

Therefore, in view of the specification, Declaration filed on March 20, 2009, and the Declaration submitted herewith, it is clear that the effect of treating human glioblastoma is supported both *in vitro* and *in vivo* with respect to Compound A, Compound B and GYKI 52466.

Applicant respectfully submits that the above-shown correlation of the claimed compounds is sufficient to show correlation of *in vitro* and *in vivo* data in commensurate in scope with currently presented claim 13. Accordingly, "[b]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence." *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). That is, even if *in vivo* data for NBQX and Talampanel are not shown, one skilled in the art would clearly envisage and predict that NBQX and Talampanel are effective *in vivo* as well, similar to the cases of Compound A, Compound B and GYKI 52466 as shown. Therefore, claim 13 is fully enabled.

While submitting the above arguments and supportive evidence solely in order to advance the prosecution of the application, Applicant does not agree with the Office's position that claim 13 lacks an enabling disclosure. The Examiner alleges that there are no *in vivo* results provided for any AMPA antagonists with the treatment of glioblastoma (Applicant submits that the Examiner is incorrect and point to Example 2 in the specification) and that there is no correlation provided between *in vitro* and *in vivo* results in terms of predictability.

Applicant submits that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." (See MPEP 2164.02). The Examiner relies on Theodora in support of her position of asserting lack of correlation based on unpredictability. (See page 5 of the Office Action). Applicant submits that this reference discusses the correlation between the results of the three types of preclinical experiments (*in vitro* human cell line, human xenograft, murine allograft) and Phase II results, with respect to four types of cancers (breast, non-small cell lung, ovary, colon). The reference only generally describes that an *in vitro* human cell line is predictive for certain types of cancers but that even *in vivo* experimental results are not always predictable (See Abstract). Theodora merely discloses common sense to one of ordinary skill in the art that good results expected based on preclinical experiments are not always obtained in clinical experiments, and a particular drug which is effective for a certain type of cancer is not always effective for other types of cancers.

Thus, while the Examiner may have pointed out unpredictability in the art, the Examiner has failed to present any evidence as to why the *in vitro* models used in the present invention do not correlate to the *in vivo* application as claimed.

In view of the above discussions and evidence, one skilled in the art would be enabled, without undue experimentation, from the guidance provided in the specification combined with the knowledge and skill available in the art to make and use the full scope of the claimed subject matter. Accordingly, the §112, first paragraph rejection of claims 13 and 18 is not sustainable and withdrawal is respectfully requested.

Response to Rejection under 35 U.S.C. § 103

On page 7 of the Action, claims 13 and 18 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Andrasi et al. (US 5,639,751) in view of Rothstein et al. (Nature Medicine, Vol. 7, No. 9, September 2001, presented in IDS).

On page 9 of the Action, claims 13 and 18 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Andrasi et al. (USP 5,639,751) in view of Takano et al., ("Glutamate release promotes growth of malignant giiomas", Nature Medicine, 7 (9), pp. 1010-1015 (2001) presented in IDS) and Catarina L. Florian et al., ("Characteristic metabolic profiles revealed by IH NMR spectroscopy for three types of brain and nervous system tumours", NMR in Biomedicine,Vol. 8, pp. 253-264 (1996) presented in IDS).

Applicant respectfully traverses.

The inventor has found that 1) the human glioblastoma cell line established by the present inventor (CGNH-89) widely expresses G1uR1 and GluR4 subunits but expresses almost no G1uR2 and GluR3, so that it functions as a Ca^{2+}-permeable AMPA receptor, 2) these described characteristics relate to highly migratory and proliferative properties of human glioblastoma, and 3) the animal model with a transplanted CGNH-89 reflects the pathological feature of human glioblastoma well, where the cell vigorously invades the inside of brain parenchyma and the subpial brain to induce meningeal dissemination. Further, the inventor confirmed that AMPA antagonists are actually effective in the above-described animal model. (See page 7, line 24 to page 8, line 15 of the specification).

To one of ordinary skill in the art, it is known that even similar cancers differ in how they are caused and that therapeutic effects on cancers differ depending not only on the type of cancer but also on the degree of malignancy. That is, as described at lines 14-17 of page 5 of the specification, the therapeutic effect on glioblastoma as in the present invention cannot be

expected from experimental results using cancer cells having a lower malignancy than glioblastoma. Further, conventional glioma studies using animal models have been criticized as they do not reproduce actual dissemination of a brain tumor and lack predictability of the effect on a human brain tumor. (See Nature Medicine, 6(4), 369-370 (2000), submitted in IDS). Thus, there had been no reasonable expectation that AMPA antagonists would be effective for glioblastoma which had been known to be the most malignant among brain tumors including glioma.

Andrasi and Rothstein fail to teach or suggest the subject matter with a reasonable expectation of success

Andrasi discloses that Talampanel is an AMPA antagonist and is useful for various diseases of the central nervous system. However, Andrasi fails to disclose the treatment of any cancers, needless to say, including giloblastoma.

The reference Rothstein is an article criticizing the reference Takano, mentioned below. Taking into consideration the disclosure of Rzeski et al. (Proc. Natl,. Acad. Sci. USA 98 6372-6377 (2001); the third citation in Rothstein et al.), the reference Rothstein discusses the possibility of NMDA receptor and AMPA receptor blockade as one method for treating brain tumors and the possibility that an NMDA antagonist and an AMPA antagonist have direct cytostatic effect on several types of cancers. However, Rothstein fails to identify any particular AMPA receptor antagonists which may be preferred and/or effective in treating glioblastoma or any other various tumor.

Furthermore, Rzeski reports the *in vitro* effects of an NMDA antagonist (MK801) and an AMPA antagonist (GYKI 52466) on various cancers including human brain astrocytoma and human medulloblastoma. However, Rzeski fails to provide any concrete description of

glioblastoma, but rather, provides a description that teaches away from the subject matter, i.e., tumors of peripheral origin responded favorably to either NMDA or AMPA antagonists, whereas those derived from neuronal and glial tissues were less sensitive to glutamate antagonists. (See page 6377, right column).

Thus it appears that the Examiner relies on hindsight in alleging that any compound which is an AMPA inhibitor useful in treating various central nervous system diseases would also be effective in treating glioblastoma.

In view of the above, the Examiner has failed to provide any rationale as to why one skilled in the art would expect that the compound of Andrasi would be useful in treating glioblastoma with any reasonable expectation or prediction of success. Accordingly, Applicant respectfully requests the reconsideration and withdrawal of the § 103 rejection of claims 13 and 18 based on Andrasi and Rothstein.

The Examiner's conclusion of obviousness in view of Andrasi, Takano, and Florian is flawed

Takano discloses that NMDA antagonists (MK801 and memantine) inhibit proliferation in the rat model transplanted with C2 and RG2 glioma (glutamate-secreting tumor cells), different from the human glioblastoma cells (CGNH-89) established by the inventor. Further, Takano fails to provide any concrete description of glioblastoma. In addition, the cited reference Rothstein criticizes Takano, specifically there is a statement questioning whether the experiments using rat-derived glioma cells such as CG and RG2 reflect human brain tumors and whether the experiments can be applied to brain tumors other than glioma. (See page 995, middle column).

Florian is directed towards a diagnosis method. In Florian, glutamate in meningioma, which is a benign brain tumor, was detected in an amount of two times or more higher than that

in glioblastoma. Further, Florian fails to establish any relationship between glutamate itself and glioblastoma and merely shows that various metabolites including glutamate were detected in glioblastoma.

The Examiner appears to assume that AMPA antagonists (Talampanel, etc.) must also be effective for treating human glioblastoma, based on the fact that 1) the NMDA antagonists used in Takano are effective for treating rat glioma, 2) glioma and glioblastoma are both glutamate-secreting tumor cells, and 3) NMDA receptors and AMPA receptors are both ionotropic glutamate receptors. However, this assumption is flawed. In fact, Applicant submits herewith results demonstrating that the NMDA antagonist (MK801) of Takano fails to inhibit proliferation of human glioblastoma cells (CGNH-89) used in the present invention. (See Test 1 of the Rule 1.132 Declaration submitted herewith).

Furthermore, as amended, claim 13 recites five specific AMPA antagonist compounds for the treatment of glioblastoma and none of Andrasi, Takano, or Florian identifies any particular AMPA receptor antagonists which may be preferred and/or effective in treating glioblastoma or any other various tumor.

Accordingly, to one of ordinary skill in the art, it is clear that the present invention was achieved only after actually confirming the effects of AMPA antagonists in treating human glioblastoma *in vitro* and/or *in vivo* using the human glioblastoma cell (CGNH-89) which was established by the present inventor.

In view of the above, Applicant respectfully requests reconsideration and withdrawal of the 35 U.S.C. § 103 rejection of claims 13 and 18 based on Andrasi, Takano, and Florian.

Request for Rejoinder of Claims 14-17

As discussed above, claim 13 (generic claim over claims 14-18) and claim 18 are patentable. Therefore, Applicant respectfully requests claims 14-17 be rejoined, because these claims are dependent from patentable claim 13. Furthermore, it is submitted that claims 14-17 are patentable for the same reasons of the patentability of claim 13 and claim 18.

CONCLUSION

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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